

What is Claimed is:

1. A mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.
2. The mixture according to Claim 1, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.
3. The mixture according to Claim 1, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.
4. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 2, 3 or 4 polyalkylene glycol subunits.
5. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 5 or 6 polyalkylene glycol subunits.
6. The mixture according to Claim 1, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.
7. The mixture according to Claim 6, wherein the polyalkylene glycol moiety is a polypropylene glycol moiety.
8. The mixture according to Claim 7, wherein the polypropylene glycol is uniform.
9. The mixture according to Claim 1, wherein the growth hormone drug is human growth hormone.
10. The mixture according to Claim 9, wherein the oligomer is covalently coupled to an amino function of the human growth hormone.

11. The mixture according to Claim 10, wherein the amino function is at an amino acid residue of the human growth hormone selected from the group consisting of Phe¹, Lys³⁸, Lys⁴¹, Lys⁷⁰, Lys¹¹⁵, Lys¹⁴⁰, Lys¹⁴⁵, Lys¹⁵⁸, Lys¹⁶⁸ and Lys¹⁷².

12. The mixture according to Claim 9, wherein the conjugate comprises a plurality of oligomers.

13. The mixture according to Claim 1, wherein the polyalkylene glycol moiety is a polypropylene glycol moiety.

14. The mixture according to Claim 13, wherein the polypropylene glycol moiety is uniform.

15. The mixture according to Claim 1, wherein the oligomer consists of a uniform polypropylene glycol moiety and wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

16. The mixture according to Claim 1, wherein the growth hormone drug is covalently coupled to the oligomer.

17. The mixture according to Claim 16, wherein the growth hormone drug is covalently coupled to the oligomer by a hydrolyzable bond.

18. The mixture according to Claim 1, wherein the growth hormone drug is covalently coupled to the polyalkylene glycol moiety.

19. The mixture according to Claim 18, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the polyalkylene glycol moiety.

20. The mixture according to Claim 1, wherein the oligomer further comprises a lipophilic moiety.

21. The mixture according to Claim 20, wherein the growth hormone drug is covalently coupled to the lipophilic moiety.

22. The mixture according to Claim 1, wherein the conjugate comprises a plurality of oligomers.

23. The mixture according to Claim 22, wherein each oligomer in the plurality of oligomers is the same.

24. The mixture according to Claim 1, wherein the oligomer comprises a first polyalkylene glycol moiety covalently coupled to the growth hormone drug by a non-hydrolyzable bond and a second polyalkylene glycol moiety covalently coupled to the first polyalkylene glycol moiety by a hydrolyzable bond.

25. The mixture according to Claim 24, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the second polyalkylene glycol moiety.

26. The mixture according to Claim 1, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

27. A pharmaceutical composition comprising:
the mixture according to Claim 1; and
a pharmaceutically acceptable carrier.

28. A method of treating growth hormone deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of a mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety,
said mixture having a molecular weight distribution with a standard deviation of less than
about 22 Daltons to the patient to treat the growth hormone deficiency.

29. A method of accelerating the growth rate of an animal, said method comprising:

administering to the animal a mixture of conjugates each comprising a growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety, said
5 mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, in an amount sufficient to accelerate the animal's growth rate.

30. A substantially monodispersed mixture of conjugates, each conjugate comprising a growth hormone drug coupled to an oligomer that comprises a polyalkylene glycol moiety.

31. The mixture according to Claim 30, wherein the polyalkylene glycol moiety has at least 2, 3 or 4 polyalkylene glycol subunits.

32. The mixture according to Claim 30, wherein the polyalkylene glycol moiety has at least 5 or 6 polyalkylene glycol subunits.

33. The mixture according to Claim 30, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

34. The mixture according to Claim 30, wherein at least about 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight.

35. The mixture according to Claim 30, wherein the mixture is a monodispersed mixture.

36. The mixture according to Claim 30, wherein the mixture is a substantially purely monodispersed mixture.

37. The mixture according to Claim 30, wherein at least about 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight and have the same molecular structure.

38. The mixture according to Claim 30, wherein the mixture is a purely monodispersed mixture.

39. The mixture according to Claim 30, wherein the polyalkylene glycol moiety is a uniform polypropylene moiety.

40. A substantially monodispersed mixture of conjugates, each conjugate comprising human growth hormone covalently coupled to an oligomer that comprises a uniform polypropylene glycol moiety having at least 7 polypropylene glycol subunits.

41. The mixture according to Claim 40, wherein the oligomer consists of a uniform polypropylene glycol moiety having at least 7 polypropylene glycol subunits, and wherein each conjugate is amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

42. A mixture of conjugates each comprising a growth hormone drug coupled to a polymer having a polyalkylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^n N_i M_i \right)^2}{\sum_{i=1}^n N_i M_i^2 \sum_{i=1}^n N_i - \left(\sum_{i=1}^n N_i M_i \right)^2}$$

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wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

43. The mixture according to Claim 42, wherein the dispersity coefficient is greater than 100,000.

44. The mixture according to Claim 42, wherein the dispersity coefficient is greater than 500,000.

45. The mixture according to Claim 42, wherein the growth hormone drug is human growth hormone.

46. The mixture according to Claim 42, wherein the polyalkylene glycol moiety is a polypropylene glycol moiety.

47. The mixture according to Claim 42, wherein the polypropylene glycol moiety is uniform.

48. The mixture according to Claim 42, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

49. A mixture of conjugates in which each conjugate: comprises a growth hormone drug coupled to an oligomer; and has the same number of polyalkylene glycol subunits.

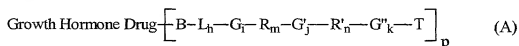
50. The mixture according to Claim 49, wherein the growth hormone drug is human growth hormone.

51. The mixture according to Claim 49, wherein the polyalkylene glycol moiety is a polypropylene glycol moiety.

52. The mixture according to Claim 51, wherein the polypropylene glycol moiety is uniform.

53. The mixture according to Claim 49, wherein the polyalkylene glycol moiety has at least 7 polyalkylene glycol subunits.

54. A mixture of conjugates in which each conjugate has the same molecular weight and has the formula:



wherein:

- 5 B is a bonding moiety;
 L is a linker moiety;
 G, G' and G'' are individually selected spacer moieties;
 R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;
- 10 T is a terminating moiety;
 h, i, j, k, m and n are individually 0 or 1, with the proviso that when R is the polyalkylene glycol moiety; m is 1, and when R' is the polyalkylene glycol moiety, n is 1; and
 p is an integer from 1 to the number of nucleophilic residues on the growth hormone
- 15 drug.

55. The mixture according to Claim 54, wherein the polyalkylene glycol group is a polypropylene glycol moiety.

56. The mixture according to Claim 55, wherein the polypropylene glycol group is uniform.

57. The mixture according to Claim 54, wherein:
 i, j, k, and n are 0;
 R is uniform polypropylene glycol; and
 the conjugates are each amphiphilically balanced such that each conjugate is
- 5 aqueously soluble and able to penetrate biological membranes.

58. The mixture according to Claim 54, wherein R is a polyalkylene glycol moiety having at least 7 polyalkylene glycol subunits.

59. A process for synthesizing a substantially monodispersed mixture of conjugates each conjugate comprising a growth hormone drug coupled to an oligomer that comprises a polyethylene glycol moiety, said process comprising:

reacting a substantially monodispersed mixture comprising compounds having the
5 structure of Formula I:



wherein R^1 is H or a lipophilic moiety; m is from 1 to 25; and X^+ is a positive
ion,

with a substantially monodispersed mixture comprising compounds having the structure of
10 Formula II:



wherein R^2 is H or a lipophilic moiety; and n is from 1 to 25,

under conditions sufficient to provide a substantially monodispersed mixture comprising
polymers having the structure of Formula III:



15 activating the substantially monodispersed mixture comprising polymers of Formula
III to provide a substantially monodispersed mixture of activated polymers capable of
reacting with a growth hormone drug; and

20 reacting the substantially monodispersed mixture of activated polymers with a
substantially monodispersed mixture of growth hormone drugs under conditions sufficient to
provide a substantially monodispersed mixture of conjugates each comprising a growth
hormone drug coupled to an oligomer that comprises a polyethylene glycol moiety with m+n
subunits.

60. The process according to Claim 59, wherein R^2 is a fatty acid moiety or an
ester of a fatty acid moiety.

61. The process according to Claim 60, wherein the fatty acid moiety or the ester
of a fatty acid moiety comprises an alkyl moiety at least 5 carbon atoms in length.

62. The process according to Claim 59, wherein R^1 is a methyl group.

63. The process according to Claim 59, further comprising:
reacting a substantially monodispersed mixture comprising compounds having the
structure of Formula V:



- 5 with a methanesulfonyl halide under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula II:



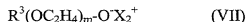
64. The process according to Claim 63, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula VI:



- 5 wherein R^2 is a lipophilic moiety;

with a substantially monodispersed mixture comprising compounds having the structure of Formula VII:



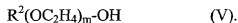
wherein R^3 is benzyl, trityl, or THP; and X_2^+ is a positive ion;

- 10 under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula VIII:



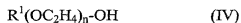
reacting the substantially monodispersed mixture comprising compounds having the structure of Formula VIII under conditions sufficient to provide a substantially

- 15 monodispersed mixture comprising compounds having the structure of Formula V:



65. The process according to Claim 59, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula IV:



- 5 under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula I:



66. The process according to Claim 59, wherein the activating of the substantially monodispersed mixture comprises reacting the substantially monodispersed mixture of

polymers of Formula III with N-hydroxy succinimide to provide an activated polymer capable of reacting with a growth hormone drug.

67. The process according to Claim 59, wherein the growth hormone drug is human growth hormone, and wherein the reacting of the substantially monodispersed mixture of activated polymers with a substantially monodispersed mixture of human growth hormone comprises:

5 reacting the substantially monodispersed mixture of activated polymers with an amino function of an amino acid residue of the human growth hormone selected from the group consisting of Phe¹, Lys³⁸, Lys⁴¹, Lys⁷⁰, Lys¹¹⁵, Lys¹⁴⁰, Lys¹⁴⁵, Lys¹⁵⁸, Lys¹⁶⁸, Lys¹⁷² and combinations thereof to provide a substantially monodispersed mixture of conjugates each comprising a human growth hormone coupled to one or more oligomers that each comprise a
10 polyethylene glycol moiety with m+n subunits.